

96298049. PubMed ID: 8709097. Inhibitors of **human immunodeficiency virus** type 1 derived from gp41 **transmembrane** protein: structure--activity studies. Kazmierski W M; Hazen R J; Aulabaugh A; StClair M H. (Department of Medicinal Chemistry I, Glaxo Wellcome Inc., Research Triangle Park, North Carolina 27709, USA.) Journal of medicinal chemistry, (1996 Jul 5) Vol. 39, No. 14, pp. 2681-9. Journal code: 9716531. ISSN: 0022-2623. Pub. country: United States. Language: English.

AB We synthesized analogues of gp41 (553-590), 1, and evaluated them for their inhibitory activity against **HIV-1** in MT4 cell assay (IC₅₀(1) = 2.7 microM). (The numbering scheme for gp41 (e.g., gp41(553-590) for 1) adapted throughout the text is from ref 6.) Gradual truncation of either the N- or C-terminal end of gp41 (553-590) resulted in a substantial loss of inhibitory properties of resulting compounds. Unexpectedly, simultaneous truncations of both N- and C-termini of gp41(553-590) resulted in a potent **heptadecamer**, 13, IC₅₀ = 10.4 microM. Coupling of a racemic alpha-aminotetradecanoic acid (Atd) to gp41 fragments afforded diastereomeric conjugates, most of which were chromatographically separable. In this series, pentadecamer 27 had an IC₅₀ of 8.9 microM, while its Atd diastereomer 28 was much less inhibitory. This finding is consistent with relative inhibitory potencies of other Atd-containing diastereomeric pairs and could reflect a chiral sense of Atd residue interacting with the receptor. Compounds 13 and 27, which are practically equipotent to 1, represent minimalistic fragments of the leucine-zipper region of gp41 and constitute a basis for design of a second generation of gp41-based inhibitors. Circular dichroism studies suggested that compounds in this series are likely to inhibit **HIV-1** replication by virtue of their alpha-helical character. The observed structure-activity relationship supports impairment of viral gp41 as a possible mechanism of action of 1.

<110> APPLICANT: Trimeris, Inc.
 <120> TITLE OF INVENTION: HIV-Derived HRI Peptides Modified to Form Stable Trimers, and
 Their Use In Therapy to Inhibit Transmission of Human
 Immunodeficiency Virus
 <130> FILE REFERENCE: TRM-001
 <140> CURRENT APPLICATION NUMBER: US/10/664,021
 <141> CURRENT FILING DATE: 2003-09-16
 <150> PRIOR APPLICATION NUMBER: US 60/414,514
 <151> PRIOR FILING DATE: 2002-09-27
 <160> NUMBER OF SEQ ID NOS: 82
 <170> SOFTWARE: PatentIn version 3.2

<210> SEQ ID NO 1
 <211> LENGTH: 59
 <212> TYPE: PRT
 <213> ORGANISM: Human immunodeficiency virus type 1
 <400> SEQUENCE: 1
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 Gln Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu Leu Gln
 20 25 30
 Leu Thr Val Trp Gly Ile Lys Gln Leu Gln Ala Arg Ile Leu Ala Val
 35 40 45
 Glu Arg Tyr Leu Lys Asp Gln Leu Leu Gly Ile
 50 55

e p g a b c d e f
 "WT" - Q Q H L L Q L T V W

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<212> TYPE: PRT

<213> ORGANISM: Human immunodeficiency virus type 1

<400> SEQUENCE: 1

```
Thr Leu Thr Val Gln Ala Arg Gln Leu Leu Ser Gly Ile Val Gln Gln
1          5          10          15
Gln Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu Leu Gln
20          25          30
Leu Thr Val Trp Gly Ile Lys Gln Leu Gln Ala Arg Ile Leu Ala Val
35          40          45
Glu Arg Tyr Leu Lys Asp Gln Leu Leu Gly Ile
50          55
```

	10	20	30	40
T-21	--NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ			
Gp41bru.pro	QQ			Q
Gp41hxb2.PRO	QQ			Q
PNL4-3 gp41.PRO	QQ			Q
Ug273-A.pro	QQS	K	L	R.Q
Us2-B.pro	QQ		V	Q
Ug268-C.pro	QQ	M	T.V.I	Q.Q
Se365-D.pro	QQ			R.Q
CM240-E.pro	QQS		V	K
Bz126-F.pro	QQ		V	Q.Q
HH8793-G.pro	QQS		V.L	R.Q
ENV_HV1BN	QQ	M	M.E	V
ENV_HV1C4	QQ	K		Q
ENV_HV1KB	QQ	D	V	Q
_VCLJH00	QQ	K		Q
ENV_HV1B8	QQ	G		Q
ENV_HV1Z8	QQ	M	V.S	Q
1	QQT.M.K		V	Q
2	QOTS		V	R.Q
3	QQ.D	M	V.L.G	Q.Q
4	QQ.M	M	V	R.Q
5	QQS.M	L.MV	V	Q
6	QQS.M	M	V	Q
7	QQX	M	V.L	R.Q
8	QQ.D	G.D.P	W	RG.Q
9	QQ.S	Q.RM	V	Q
10	QQ.D		R	V.L.R.Q
11	QQT.M		S	V
12	QRS	K.QMWR	F	L
13	QQ	M	R.V	I
14	QQS		PG	Q
15	QQ		V	K.R.Q
16	ER.K.R	M	V	S
17	HQS		V	R.Q
18	QQ.D	G.D.P	V	V.RG.Q

FIG. 2

IV

HIV-1/SIVcpz proteins

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Gag	470
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Construction of HIV-1/SIVcpz protein alignments

The number of full-length gene sequences is still growing rapidly for all genes. The envelope master alignment now contains 307 full-length sequences. For the purposes of the printed alignments, we have had to limit the number of sequences dramatically. Here we list the criteria we have followed to make the selection.

First, we have decided to end the supremacy of the B clade sequences. More than half (198, to be precise) of the full-length envelope sequences are still subtype B, though the contribution of other subtypes is increasing. We have tried to balance the number of representatives of all subtypes in these alignments. For this, we had to make a heavy selection on subtype B sequences. We have tried to include as many “classical” sequences as possible. A lot of follow-up work has been done based on lab strains such as HXB2, MN, SF2, and JR-CSF/JR-FL, so these strains are included in the alignments. Furthermore, within subtype B we have tried to represent sequences from diverse geographical origins, so as to represent a broad spectrum of variants. In the case of subtype B, this means that we have included African, Asian and Brazilian variants along with the “Western” strains. For sequences from non-B subtypes, we have selected a few representative sequences from each dataset, again with an eye on maintaining geographical diversity. When possible we have left all representatives of group O in the alignment, as these sequences are much more genetically diverse than the subtypes.

 Explanation of Symbols in Alignments

Symbol	Meaning
--------	---------

Alignment symbols

? in consensus	no majority-rule consensus could be determined at this position
x	nucleotide missing from codon
#	frameshift, or codon contains N or illegal character
\$	stop codon

Annotation symbols

-	domain boundaries
/	protein start point
\	protein end point
∨	splice site or exon join
->	start of overlapping coding region
<-	end of overlapping coding region
*	cysteine
^^ [NxS, NxT]	glycosylation site
^^ [NCS, NCT]	glycosylation site with cysteine
CD4	residue critical for CD4 binding
cds	coding sequence (indicates regions where two proteins overlap; the overlapping proteins use two different reading frames)
MHR	major homology region
nls	nuclear localization signal
phos site	phosphorylation site
PKC	protein kinase C binding
Zn-motif	Zinc finger binding motif

Sources of Annotation in the Alignments

Protein	Annotation	Reference
Gag	phos site Ser (111)	Yu, J Biol Chem 270:4792 (1995)
Gag	MHR, (284-302)	Otteken, J Virol 70:3407 (1996)
Gag	CyPa (205-241)	Braaten, J Virol 70:4220 (1996)
Gag	vpr packaging domain	Lu, J Virol 69:6873 (1995)
	LKSLFG, (489-494)	Kondo, J Virol 70:159 (1996)
Nef	myristylation, (1-7)	Huang, J Virol 69:93 (1995)
Nef	MHC downmodulation, PK recruitment (26-29)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Nef	heart of CD4 binding site (55-56)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Nef	acidic cluster, (60-64)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Nef	(PxxP)3, (67-76)	Huang, J Virol 69:93 (1995)
Nef	PKC, (75-80)	Huang, J Virol 69:93 (1995)
Nef	polypurine tract, (89-97)	Huang, J Virol 69:93 (1995)
Nef	PAK binding, (103-105)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Nef	Beta turn, (128-131)	Huang, J Virol 69:93 (1995)
Nef	PxxP, (145-148)	Huang, J Virol 69:93 (1995)
Nef	COP1 recruitment (152-153)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Nef	AP recruitment, (162-163)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Nef	V-ATPase and Raf-1 binding, (172-173)	Piguet, p. 448 Human Retroviruses and AIDS (1999)
Vpr	alpha helix, (16-34)	Cornelissen, ARHR 13:247 (1997)
Vpr	H(S/F)RIG motifs, (71-82)	Macreadie, PNAS USA 92:2770 (1995)
Vpu	all annotations	Cornelissen, ARHR 13:247 (1997)
Vpr	LR domain, (60-82)	Wang, Gene 178:7 (1996)

Table 1: Table of HIV-1/SIVcpz protein Alignments

Name	Accession	Region	Author	Reference
A.DE.AF200476	AF200476	VIF	Kuhn, J	Unpublished
A.FR.HIV232956	AJ232956	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
A.GB.MA246	Y13718	ENV	Douglas, NW	J Mol Biol 273(1):122-149 (1997)
A.KE.AF233689	AF233689	VIF	Kuhn, J	Unpublished
A.KE.K89	L22943	ENV	Louwagie, J	J Virol 69(1):263-271 (1995)
A.KE.Q23	AF004885	ENV GAG NEF POL REV TAT VIF VPR VPU	Poss, M	Unpublished
A.RW.PVP1	L07082	ENV	Bex, F	Unpublished (1992)
A.SE.SE6594	AF069672	GAG NEF POL REV TAT VIF VPR VPU	Carr, JK	AIDS 13(14):1819-1826 (1999)
A.SE.SE7253	AF069670	GAG POL REV TAT VIF VPR VPU	Carr, JK	AIDS 13(14):1819-1826 (1999)
A.SE.SE7535	AF069671	GAG POL REV TAT VIF VPR	Carr, JK	AIDS 13(14):1819-1826 (1999)
A.SE.SE8538	AF069669	GAG NEF POL REV TAT VIF VPR	Carr, JK	AIDS 13(14):1819-1826 (1999)
A.SE.SE8891	AF069673	GAG NEF REV TAT VIF VPR	Carr, JK	AIDS 13(14):1819-1826 (1999)
A.SE.UGSE8131	AF107771	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukkanen, T	-
A.UA.ukr970063	AF082486	ENV REV VPU	Liitsola, K	AIDS 12(14):1907-1919 (1998)
A.UG.92UG037	U51190	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 70(3):1651-1657 (1996)
A.UG.U13-2	X91354	VIF	Wieland, U	J Gen Virol 78:393-400 (1997)
A.UG.U455	M62320	ENV GAG NEF POL REV TAT VPR VPU	Oram, JD	ARHR 6(9):1073-1078 (1990)
A.UG.UG273A	L22957	REV TAT VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
A.UG.UG275A	L22951	REV TAT VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
A2.CD.97CDKFE4	AF286240	POL VIF VPR	Gao, F	ARHR 17(8):675-688(2001)
A2.CD.97CDKS10	AF286241	ENV REV TAT VIF VPR VPU	Gao, F	ARHR 17(8):675-688(2001)
A2.CD.97CDKTB48	AF286238	ENV GAG NEF REV TAT VIF VPR VPU	Gao, F	ARHR 17(8):675-688(2001)
A2.CY.94CY017-41	AF286237	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	ARHR 17(8):675-688(2001)

Table 1: cont.

Name	Accession	Region	Author	Reference
B.AU.MBC18	AF042102	ENV GAG POL REV VIF VPR VPU	Oelrichs, RB	ARHR 14(9):811-814 (1998)
B.AU.MBC200	AF042100	NEF TAT	Oelrichs, RB	ARHR 14(9):811-814 (1998)
B.AU.SC49	AF128998	GAG	Oelrichs, RB	Unpublished
B.AU.VH	AF146728	GAG REV VPR VPU	Oelrichs, R	Unpublished
B.CN.RL42	U71182	ENV GAG NEF POL REV TAT VIF VPR VPU	Graf, M	ARHR 14(3):285-288 (1998)
B.DE.D31	U43096	ENV GAG NEF POL REV TAT VIF VPR VPU	Kreutz, R	ARHR 8(9):1619-1629 (1992)
B.DE.HAN	U43141	ENV GAG NEF REV	Sauermann, U	ARHR 6(6):813-823 (1990)
B.ES.89SP061	AJ006287	ENV GAG NEF REV TAT VIF VPR VPU	Olivares, I	ARHR 14(18):1649-165 (1998)
B.FR.HXB2	K03455	ENV GAG NEF POL REV TAT VIF VPR VPU	Wong-Staal, F	Nature 313(6000):277-284 (1985)
B.FR.NE100	M58272	NEF	Delassus, S	J Virol 65:225-231 (1991)
B.FR.SWB884	M58206	NEF	Delassus, S	J Virol 65:225-231 (1991)
B.FR.vi02011A1H	AF143115	VIF	Hassaine, G	Virology 276(1):169-180 (2000)
B.GA.OY1	M26727	ENV GAG NEF POL REV TAT VIF VPR VPU	Huet, T	AIDS 3(11):707-715 (1989)
B.GB.CAM1	D10112	ENV GAG NEF POL REV TAT VIF VPR VPU	McIntosh, AA	Unpublished (1991)
B.GB.GB8	AJ271445	GAG	Farrar, GH	J Med Virol 34(2):104-113 (1991)
B.GB.I4663	Z68564	VPR	Kuiken, CL	J Gen Virol 77(Pt 4):783-792 (1996)
B.GB.I4663	Z68613	VPU	Kuiken, CL	J Gen Virol 77(Pt 4):783-792 (1996)
B.GB.MANC	U23487	GAG	Zhu, T	Nature 374(6522):503-504 (1995)
B.GB.WB	U36882	ENV	Douglas, NW	AIDS 10(1):39-46 (1996)
B.IN.HIVP35A	Y15122	NEF	Ahmad, KM	ARHR 14(16):1491-1493 (1998)
B.IT.B-IT-R5	AF147737	NEF	Catucci, M	J Med Virol 60(3):294-299 (2000)
B.JP.D70887	D70887	VIF	Tominaga, K	ARHR 12(16):1543-1549 (1996)
B.JP.ETR	D12582	ENV	Shimizu, H	Virology 189:534-546 (1992)
B.JP.JH31	M21137	GAG	Komiyama, N	ARHR 5:411-419 (1989)
B.JP.JH32	M21138	ENV VPU	Komiyama, N	ARHR 5:411-419 (1989)
B.JP.PT1-01	AB034578	VPU	Yamada, T	Arch Virol 145(5):1021-1027 (2000)
B.JP.PT1-4	AB034517	VPR	Yamada, T	Arch Virol 145(5):1021-1027 (2000)
B.JP.PT7-6	AB034474	VIF	Yamada, T	Arch Virol 145(5):1021-1027 (2000)

Table 1: cont.

Name	Accession	Region	Author	Reference
B.JP.nsf<7>-a	AB034272	NEF	Yamada, T	Arch Virol 145(5):1021-1027 (2000)
B.KR.CSR9412d	AF238268	NEF	Cho, YK	Unpublished
B.KR.WK	AF224507	ENV GAG NEF POL REV TAT VIF VPR VPU	Cho, YK	Unpublished
B.NL.3202A21	U34604	ENV GAG NEF POL REV TAT VIF VPR VPU	Guillon, C	ARHR 11(12):1537-1541 (1995)
B.SE.AF047085	AF047085	NEF	Visco Comandini, U	J Hum Virol 1(5):320-327 (1998)
B.TH.28-19	U48917	NEF	Artenstein, AW	ARHR 12:557-560 (1996)
B.TH.93TH067	U39258	ENV	Penny, MA	ARHR 12(8):741-747 (1996)
B.TH.AF082839	AF082839	NEF	Vallejo, A	AIDS 13(4):532-534 (1999)
B.TT.QZ4589	U32396	ENV	Blattner, W	Unpublished (1995)
B.TW.TWB101	AF220464	VPU	Lee, CN	J Clin Microbiol 38(7):2468-2474 (2000)
B.TW.TWCYS	AF086817	ENV GAG NEF POL REV TAT VIF VPR VPU	Huang, LM	Unpublished
B.UA.UKR1216	AF193278	ENV REV VPU	Liitsola, K	ARHR 16(11):1047-1053 (2000)
B.US.I-2	U41181	VIF	Sova, P	J Virol 69(4):2557-2564 (1995)
B.US.85WCIPR54	U69584	GAG	Fang, G	J AIDS 12(4): 352-357 (1996)
B.US.AD8	AF004394	GAG	Theodore, TS	ARHR 12(3): 191-194 (1996)
B.US.AF019528	AF019528	VIF	Yedavalli, VR	J Virol 72(2):1092-1102 (1998)
B.US.BC	L02317	VIF	Ghosh, SK	Virology 194, 858-864 (1993)
B.US.DH123	AF069140	ENV GAG	Shibata, R	J Virol 69(7):4453-4462 (1995)
B.US.JRCSF	M38429	ENV GAG NEF POL REV TAT VIF VPR VPU	O'Brien, WA	Nature 348:69-73 (1990)
B.US.JRFL	U63632	ENV GAG NEF POL REV TAT VIF	O'Brien, WA	Nature 348:69-73 (1990)
B.US.LM1	U16909	NEF	Huang, Y	J Virol 69(1):93-100 (1995)
B.US.MNCG	M17449	ENV GAG NEF POL REV TAT VIF VPR VPU	Gurgo, C	Virology 164(2):531-536 (1988)
B.US.NC7	AF049495	NEF	Mwaengo, DM	J Virol 72(11):8976-8987 (1998)
B.US.NY5CG	M38431	GAG	Willey, RL	PNAS USA 83(14):5038-5042 (1986)
B.US.RF	M17451	ENV GAG NEF POL REV TAT VIF VPR VPU	Starich, BR	Cell 45(5):637-648 (1986)
B.US.SC	M17450	REV	Gurgo, C	Virology 164(2):531-536 (1988)
B.US.SF2	K02007	ENV GAG NEF POL REV VIF VPR VPU	van Beveren, CP	RNA tumor viruses, 2nd edition, Vol 2: 1124-1141; Cold Spring Harbor Laboratory (1985)

Table 1: cont.

Name	Accession	Region	Author	Reference
B.US.WC001	AF003887	REV TAT VIF VPR VPU	Fang, G	J AIDS 12(4):352-357 (1996)
C.BI.BU910112	U39233	ENV	Penny, MA	ARHR 12(8):741-747 (1996)
C.BR.92BR025	U52953	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 70(3):1651-1667 (1996)
C.BW.96BW01B03	AF110959	POL	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW01B21	AF110960	NEF REV VIF VPR	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW01B22	AF110961	GAG TAT	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW0402	AF110962	ENV GAG NEF POL REV TAT VIF VPR VPU	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW0502	AF110967	GAG NEF POL	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW0504	AF110968	REV TAT VIF VPR	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW1104	AF110969	GAG NEF POL REV VIF	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW1210	AF110972	GAG REV	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW15B03	AF110973	GAG REV	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW1626	AF110978	GAG	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW16B01	AF110976	REV	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.BW.96BW17A09	AF110979	GAG REV	Novitsky, VA	J Virol 73(5):4427-4432 (1999)
C.CN.AF268277	AF268277	ENV	Chen, Z	J Virol 74(14):6501-6510 (2000)
C.DJ.DJ259A	L22940	REV TAT VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
C.DJ.DJ373A	L23065	ENV REV TAT	Louwagie, J	J Virol 69(1):263-271 (1995)
C.ET.ETH2220	U46016	ENV GAG NEF POL REV TAT VIF VPR VPU	Salminen, MO	ARHR 12(14):1329-1339 (1996)
C.FR.HIV232980	AJ232980	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
C.FR.HIV232996	AJ232996	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
C.IN.93IN101	AB023804	ENV GAG NEF REV TAT VPR VPU	Mochizuki, N	ARHR 15(14):1321-1324 (1999)
C.IN.93IN904	AF067157	GAG NEF	Lole, KS	J Virol 73(1):152-160 (1999)
C.IN.93IN905	AF067158	GAG	Lole, KS	J Virol 73(1):152-160 (1999)
C.IN.93IN999	AF067154	GAG NEF POL	Lole, KS	J Virol 73(1):152-160 (1999)
C.IN.94IN11246	AF067159	GAG NEF POL REV TAT VIF VPR	Lole, KS	J Virol 73(1):152-160 (1999)
C.IN.95IN21068	AF067155	GAG NEF POL REV TAT VIF VPR	Lole, KS	J Virol 73(1):152-160 (1999)
C.IN.AF209990	AF209990	GAG	Gupta, S	Protein Expr Purif 21(7):378-385 (2001)
C.IN.HIVY15117	Y15117	NEF	Ahmad, KM	ARHR 14(16):1491-1493 (1998)

Table 1: cont.

Name	Accession	Region	Author	Reference
C.IN.HIVY17884	Y17884	NEF	Ahmad, KM	ARHR 14(16):1491-1493 (1998)
C.IN.HIVY17891	Y17891	NEF	Ahmad, KM	ARHR 14(16):1491-1493 (1998)
C.IN.HIVY17892	Y17892	NEF	Ahmad, KM	ARHR 14(16):1491-1493 (1998)
C.SN.SE364A	L22944	VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
C.SO.S0145A	L22946	ENV REV VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
C.TW.TWC2	AF220473	VPU	Lee, CN	J Clin Microbiol 38(7):2468-2474 (2000)
C.UG.UG268A2	L22948	ENV REV VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
D.CD.84ZR085	U88822	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 72(7):5680-5698 (1998)
D.CD.ELI	K03454	ENV GAG NEF POL REV TAT VIF VPR VPU	Alizon, M	Cell 46(1):63-74 (1986)
D.CD.JY1	J03653	ENV	Younno, J	ARHR 4:165-173 (1988)
D.CD.NDK	M27323	ENV GAG NEF POL REV TAT VIF VPR VPU	Spire, B	Gene 81:275-284 (1989)
D.CD.Z2Z6	M22639	GAG POL REV TAT VIF VPR	Srinivasan, A	Gene 52:71-82 (1987)
D.CI.CI13	AJ277820	ENV	Beirnaert, E	Virology 281(2):305-314 (2001)
D.JP.PT144	AB034541	VPR	Yamada, T	Arch Virol 145(5):1021-1027 (2000)
D.SN.SE365A2	L22945	ENV REV TAT VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
D.TZ.87TZ4622	U65075	ENV	Robbins, KE	ARHR 12(14):1389-1391 (1996)
D.TZ.TZ005	U12406	VPU	Siwka, W	ARHR 10(12):1753-1754 (1994)
D.UG.92UG024-D	U08805	ENV	WHO Global Programme	ARHR 10(11):1327-1343 (1994)
D.UG.94UG1141	U88824	GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 72(7):5680-5698 (1998)
D.UG.U18-0	X91355	VIF	Wieland, U	J Gen Virol 78:393-400 (1997)
D.UG.U25-6	X91361	VIF	Wieland, U	J Gen Virol 78:393-400 (1997)
D.UG.U36-0	X91363	VIF	Wieland, U	J Gen Virol 78:393-400 (1997)
D.UG.UG266A2	L22947	VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
D.UG.UG269A	L22949	REV	Louwagie, J	J Virol 69(1):263-271 (1995)
D.UG.UG274A2	L22950	REV TAT	Louwagie, J	J Virol 69(1):263-271 (1995)
D.UG.WHO15-474	U36886	ENV	Douglas, NW	AIDS 10(1):39-46 (1996)
D.ZR.AF233690	AF233690	VIF	Kuhn, J	Unpublished
F.I.BE.VI850	AF077336	ENV GAG NEF POL REV TAT VIF VPR VPU	Carr, JK	Virology 269(1):95-104 (2000)

Table 1: cont.

Name	Accession	Region	Author	Reference
F1.BR.93BR020-1	AF005494	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 72(7):5680-5698 (1998)
F1.BR.BZ126	L22082	ENV REV TAT VPU	Louwagie, J	ARHR 10(5):561-567 (1994)
F1.BR.BZ162	L11751	GAG	Louwagie, JJ	AIDS 7:769-780 (1993)
F1.BR.BZ163	L22085	REV TAT VPU	Louwagie, J	ARHR 10(5):561-567 (1994)
F1.CD.V1174	L11782	GAG	Louwagie, JJ	AIDS 7:769-780 (1993)
F1.DE.AF200475	AF200475	VIF	Kuhn, J	Unpublished
F1.FI.FIN9363	AF075703	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukanen, T	Unpublished
F1.FR.MP411	AJ249238	ENV GAG NEF POL REV TAT VIF VPR VPU	Peeters, M	ARHR 16(2):139-151(2000)
F1.RW.V169	L11796	GAG	Louwagie, JJ	AIDS 7:769-780 (1993)
F2.CM.CA20	AJ277824	ENV	Nyambi, PN	J Virol 70(9):6235-6243 (1996)
F2.CM.HIM277819	AJ277819	ENV	Beirnaert, E	Virol 281(2):305-314 (2001)
F2.CM.HIV232985	AJ232985	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
F2.CM.MP255	AJ249236	ENV GAG POL REV TAT VIF VPR VPU	Peeters, M	ARHR 16(2):139-151(2000)
F2.CM.MP257	AJ232986	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
F2.CM.MP257	AJ249237	ENV GAG POL REV TAT VIF VPR VPU	Peeters, M	ARHR 16(2):139-151(2000)
G.BE.DRCBL	AF084936	ENV GAG NEF POL REV TAT VIF VPR VPU	Debyser, Z	ARHR 14(5):453-459 (1998)
G.CG.CNG30	AF056186	VIF VPR VPU	Harada, Y	Unpublished
G.FI.HH8793-1-1	AF061640	GAG NEF POL REV VIF VPR	Salminen, MO	ARHR 8(9):1733-1742 (1992)
G.FI.HH8793-12-1	AF061641	ENV TAT VPU	Salminen, MO	ARHR 8(9):1733-1742 (1992)
G.GA.LBV217	U09664	ENV	Janssens, W	ARHR 10:877-879 (1994)
G.ML.HIV232990	AJ232990	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
G.NG.92NG083	U88826	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 72(7):5680-5698 (1998)
G.NG.IKCSW22	AJ232991	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
G.NG.MACSW39	AJ232992	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
G.NG.NG1937	AF069937	ENV	McCutchan, FE	Virology 254(2):226-234 (1999)
G.NG.NG1939	AF069935	ENV	McCutchan, FE	Virology 254(2):226-234 (1999)
G.SE.SE6165	AF061642	ENV GAG NEF POL REV TAT VIF VPR VPU	Carr, JK	Virology 247(1):22-31 (1998)

Table 1: cont.

Name	Accession	Region	Author	Reference
G.TW.TWGI	AF220486	VPU	Lee, CN	J Clin Microbiol 38(7):2468-2474 (2000)
H.BE.V1991	AF190127	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukkanen, T	AIDS 14(11):1533-1543 (2000)
H.BE.V1997	AF190128	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukkanen, T	AIDS 14(11):1533-1543 (2000)
H.CD.HIV232994	AJ232994	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
H.CD.HIV232995	AJ232995	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
H.CF.90CF056	AF005496	ENV GAG NEF POL REV TAT VIF VPR VPU	Murphy, E	ARHR 9(10):997-1006 (1993)
J.SE.SE7022	AF082395	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukkanen, T	ARHR 15(3):293-297 (1999)
J.SE.SE7887	AF082394	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukkanen, T	ARHR 15(3):293-297 (1999)
K.BE.V1325	L11789	GAG	Louwagie, JJ	AIDS 7:769-780 (1993)
K.CD.EQTB11C	AJ249235	ENV GAG NEF POL REV TAT VIF VPR VPU	Peeters, M	ARHR 16(2):139-151 (2000)
K.CM.MP535	AJ249239	ENV GAG NEF POL REV TAT VIF VPR VPU	Peeters, M	ARHR 16(2):139-151 (2000)
N.CM.YBF106	AJ271370	ENV GAG NEF POL REV TAT VIF VPR	Souquiere, S	Unpublished
N.CM.YBF30	AJ006022	ENV GAG NEF POL REV TAT VIF VPR VPU	Simon, F	Nature Med 4(9):1032-1037 (1998)
O.CM.ANT70	L20587	ENV GAG NEF POL REV TAT VIF VPR VPU	Vanden Haesevelde, M	J Virol 68(3):1586-1596 (1994)
O.CM.CM4974	AF009033	ENV	Korber, BT	Unpublished
O.CM.HIV1CA9EN	X96522	ENV	Janssens, W	AIDS 13:41-48 (1999)
O.CM.MVP5180	L20571	ENV GAG NEF POL REV TAT VIF VPR VPU	Gurtler, LG	J Virol 68:1581-1585 (1994)
O.FR.HIVY16019	Y16019	VIF VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16020	Y16020	VIF VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16021	Y16021	VIF VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16022	Y16022	VIF VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16023	Y16023	VIF VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16024	Y16024	VIF VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16025	Y16025	VPR	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16026	Y16026	VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)

Table 1: cont.

Name	Accession	Region	Author	Reference
O.FR.HIVY16027	Y16027	VPR	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16028	Y16028	VPR	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16029	Y16029	VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16030	Y16030	VPR	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.FR.HIVY16031	Y16031	VPR VPU	Bibollet-Ruche, F	ARHR 14(11):951-961 (1998)
O.GA.VI686	X96526	ENV	Delaporte, E	AIDS 10(8):903-910 (1996)
O.GQ.193HA	U82990	ENV	Hunt, JC	ARHR 13(12):995-1005 (1997)
O.SN.MP1299	AJ302646	GAG NEF POL REV TAT VIF VPR VPU	Peeters, M	Unpublished (2000)
O.SN.MP1300	AJ302647	ENV GAG NEF POL REV TAT VIF VPR VPU	Peeters, M	Unpublished (2000)
CPZ.CD.CPZANT	U42720	ENV GAG NEF POL REV TAT VIF VPR VPU	Vanden Haesevelde, MM	Virology 221(2):346-350 (1996)
CPZ.CM.CAM3	AF115393	ENV GAG NEF POL REV TAT VIF VPR VPU	Corbet, S	J Virol 74:529-534 (2000)
CPZ.CM.CAM5	AJ271369	ENV GAG NEF POL REV TAT VIF VPR VPU	Souquiere, S	Unpublished
CPZ.GA.CPZGAB	X52154	ENV GAG NEF POL REV TAT VIF VPR VPU	Huet, T	Nature 345(6273):356-359 (1990)
CPZ.US.CPZUS	AF103818	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	Nature 397(6718):436-441 (1999)
01_AE.CF.90CF11697	AF197340	ENV GAG NEF POL REV TAT VIF VPR VPU	Anderson, JP	J Virol 74(22):10752-10765 (2000)
01_AE.CF.90CF402	U51188	ENV GAG NEF POL REV TAT VIF VPR VPU	Gao, F	J Virol 70(10):7013-7029 (1996)
01_AE.CF.90CF4071	AF197341	ENV GAG NEF POL REV TAT VIF VPR VPU	Anderson, JP	J Virol 74(22):10752-10765 (2000)
01_AE.CM.CA10	AJ277818	ENV	Beirmaert, E	Virology 281(2):305-314 (2001)
01_AE.DE.K08DE	AF215859	VIF	Kuhn, J	Unpublished
01_AE.FR.HIV232982	AJ232982	NEF	Jubier-Maurin, V	ARHR 15(1):23-32 (1999)
01_AE.TH.93TH057	AF197338	GAG NEF POL REV TAT VIF VPU	Anderson, JP	J Virol 74(22):10752-10765 (2000)
01_AE.TH.93TH065	AF197339	ENV GAG POL REV TAT	Anderson, JP	J Virol 74(22):10752-10765 (2000)
01_AE.TH.93TH253	U51189	POL REV TAT	Gao, F	J Virol 70(10):7013-7029 (1996)
01_AE.TH.93TH902	AF170549	GAG POL VPR	Chang, SY	ARHR 15(17):1591-1596 (1999)
01_AE.TH.94TH702	AF170545	POL VPR	Chang, SY	ARHR 15(17):1591-1596 (1999)

Table 1: cont.

Name	Accession	Region	Author	Reference
01_AE.TH.94TH7091	AF170546	GAG	Chang, SY	ARHR 15(17):1591-1596 (1999)
01_AE.TH.95TNIH047	AB032741	GAG POL REV TAT VIF VPR VPU	Auwanit, W	Unpublished (1999)
01_AE.TH.98-4	U48934	NEF	Artenstein, AW	ARHR 12:557-560 (1996)
01_AE.TH.CM240	U54771	ENV GAG NEF POL REV TAT VIF VPR VPU	Carr, JK	J Virol 70(9):5935-5943 (1996)
01_AE.TH.KH03	U48264	ENV	McCutchan, FE	J Virol 70(6):3331-3338 (1996)
01_AE.TH.TH022	AB032740	ENV GAG NEF POL REV TAT VIF VPR VPU	Auwanit, W	Unpublished (1999)
01_AE.TW.TWE13	AF220479	VPU	Lee, CN	J Clin Microbiol 38(7):2468-2474 (2000)
01_AE.TW.TWE6	AF220478	VPU	Lee, CN	J Clin Microbiol 38(7):2468-2474 (2000)
02_AG.CM.MP807	AJ286133	NEF POL REV TAT VIF VPR VPU	Montavon, C	J AIDS 23(5):363-374 (2000)
02_AG.DJ.DJ258A	L22939	VPU	Louwagie, J	J Virol 69(1):263-271 (1995)
02_AG.FR.DJ263	AF063223	ENV GAG NEF POL REV TAT VIF VPR VPU	Carr, JK	Virology 247(1):22-31 (1998)
02_AG.FR.DJ264	AF063224	ENV GAG NEF POL REV TAT VIF VPR VPU	Carr, JK	Virology 247(1):22-31 (1998)
02_AG.GH.G829	AF184155	GAG NEF POL REV TAT VIF VPR VPU	Candotti, D	J Med Virol 62(1):1-8 (2000)
02_AG.NG.IBNG	L39106	ENV GAG NEF POL REV TAT VIF VPR VPU	Howard, TM	ARHR 10(12):1755-1757 (1994)
02_AG.NG.NG1921	AF069941	ENV	McCutchan, FE	Virology 254(2):226-234 (1999)
02_AG.SE.SE7812	AF107770	ENV GAG NEF POL REV TAT VIF VPR VPU	Laukkanen, T	Unpublished
02_AG.SN.MP1211	AJ251056	ENV GAG NEF POL REV TAT VIF VPR VPU	Toure-Kane, C	ARHR 16(6):603-609 (2000)
02_AG.SN.MP1213	AJ251057	NEF POL REV TAT VIF VPR	Toure-Kane, C	ARHR 16(6):603-609 (2000)
03_AB.RU.KAL153-2	AF193276	ENV GAG NEF POL REV TAT VIF VPR VPU	Liitsola, K	AIDS 12(14):1907-1919 (1998)
03_AB.RU.KAL68-1	AF082485	ENV	Liitsola, K	AIDS 12(14):1907-1919 (1998)
03_AB.RU.RU98001	AF193277	ENV GAG NEF POL REV TAT VIF VPR VPU	Liitsola, K	ARHR 16(11):1047-1053 (2000)
04_cpx.CY.94CY032-3	AF049337	ENV GAG NEF POL REV	Gao, F	J Virol 72(12):10234-10241 (1998)

Table 1: cont.

Name	Accession	Region	Author	Reference
04_cpx.GR.97PVCH	AF119820	TAT VIF VPR VPU ENV GAG NEF POL REV	Nasioulas, G	ARHR 15(8):745-758 (1999)
04_cpx.GR.97PVMY	AF119819	TAT VIF VPR VPU ENV GAG NEF POL REV	Nasioulas, G	ARHR 15(8):745-758 (1999)
05_DF.BE.VI1310	AF193253	TAT VIF VPR VPU ENV GAG NEF POL REV	Laukkanen, T	Virology 269(1):95-104 (2000)
05_DF.BE.VI961	AF076998	TAT VIF VPR VPU ENV GAG NEF POL REV	Carr, JK	Virology 269(1):95-104 (2000)
06_cpx.AU.BFP90	AF064699	TAT VIF VPR VPU ENV GAG NEF POL REV	Oelrichs, RB	ARHR 14(16):1495-1500 (1998)
06_cpx.ML.95ML127	AJ288982	TAT VIF VPR VPU ENV GAG NEF POL REV	Montavon, C	ARHR 15(18):1707-1712 (1999)
06_cpx.ML.95ML84	AJ245481	TAT VIF VPR VPU ENV GAG NEF POL REV	Montavon, C	ARHR 15(18):1707-1712 (1999)
06_cpx.NG.NG3670a	AF069934	ENV ENV GAG NEF POL REV	McCutchan, FE	Virology 254(2):226-234 (1999)
06_cpx.SN.97SE1078	AJ288981	TAT VIF VPR VPU ENV GAG NEF POL REV	Montavon, C	ARHR 15(18):1707-1712 (1999)
10_CD.BFL061	AF289548	ENV GAG NEF POL REV TAT VIF VPR VPU	Kouliniska, IN	ARHR 20(5):423-431(2001)
10_CD.BFL071	AF289549	TAT VIF VPR VPU ENV GAG NEF POL REV	Kouliniska, IN	ARHR 20(5):423-431(2001)
10_CD.BFL110	AF289550	TAT VIF VPR VPU ENV GAG NEF POL REV	Kouliniska, IN	ARHR 20(5):423-431(2001)
11_cpx.CM.CA1	AJ277823	ENV ENV GAG NEF POL REV	McCutchan, FE	Virology 254(2):226-234 (1999)
11_cpx.CM.MP818	AJ291718	TAT VIF VPR VPU ENV GAG NEF POL REV	Peeters, M	Unpublished (2000)
11_cpx.FR.MP1298	AJ291719	ENV GAG NEF POL REV TAT VIF VPR VPU	Peeters, M	Unpublished (2000)
11_cpx.FR.MP1307	AJ291720	TAT VIF VPR VPU ENV GAG NEF POL REV	Peeters, M	Unpublished (2000)
11_cpx.GR.GR17	AF179368	TAT VIF VPR VPU ENV GAG NEF POL REV	Paraskevis, D	ARHR 16(9):845-855 (2000)
11_cpx.NG.NG3670b	AF069945	TAT VIF VPR VPU ENV	McCutchan, FE	Virology 254(2):226-234 (1999)

	CD4	I	V5	-I	gp120	gp41	fusion peptide	
B. FR HB2	TRDGSN	569
C. BE DCRBL	533
G. FI. HB8793-12-1	560
G. GA. L8V217	556
G. NG. 92NG083	570
G. NG. NG1937	555
G. NG. NG1937	576
G. SE. S66165	559
H. BE. V1991	572
H. CF. 90CF056	568
J. SE. S87022	561
J. SE. S87887	566
K. CD. EGTB11C	564
K. CM. MP535	561
N. CM. YBF106	555
N. CM. YBF30	540
CONSENSUS O	557
O. CM. ANT70	536
O. CM. CM4974	567
O. CM. HIV1CA9EN	578
O. CM. MP5180	577
O. GA. V1686	578
O. GO. 193HA	577
O. SN. M1300	564
CP2. US. CP2US	575
CONSENSUS 01	541
01 AE. CF. 90CF11697	548
01 AE. CF. 90CF402	569
01 AE. CF. 90CF4071	577
01 AE. CM. C40	564
01 AE. TH. 93TH065	575
01 AE. TH. CM240	560
01 AE. TH. KH03	563
01 AE. TH. TH022	564
CONSENSUS 02	563
02 AG. FR. D1263	549
02 AG. FR. D1264	575
02 AG. NG. TBNG	561
02 AG. NG. NG1921	560
02 AG. SE. S87612	579
02 AG. SN. MP1211	572
03 AB. RU. KAL153-2	566
03 AB. RU. KAL153-1	553
03 AB. RU. R098001	552
04 CD. CY. 94CY032-3	551
04 CD. GR. 97FVCH	567
04 CD. GR. 97FVCH	568
05 DF. BE. V11310	574
05 DF. BE. V1961	574
06 CD. AU. BFP90	566
06 CD. ML. 95ML127	572
06 CD. ML. 95ML84	572
06 CD. NG. NG1670a	553
06 CD. SN. 97SE1078	553
10 CD. BFL061	551
10 CD. BFL071	551
10 CD. BFL110	561
CONSENSUS 11 cpx	561
11 CD. CM. MP818	559
11 CD. CM. CA1	558
11 CD. FR. MP1298	560
11 CD. FR. MP1307	567
11 CD. GR. GR17	557
CP2. CM. CAM3	555
CP2. CD. CP2ANT	561
CP2. CM. CAM5	562
CP2. GA. CP2GAB	567

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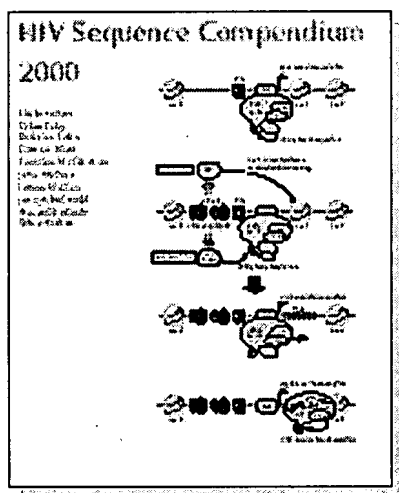
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WMGKQIARILAVRYLQDQQLLWGWGCGKGLKLTATVPWNASWS N	VI-V	V-L	V-R	V-I	V-N	V-S	V-A	V-E	V-Q	V-K	V-J	V-H	V-G	V-F	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X	V-W	V-V	V-U	V-T	V-S	V-R	V-Q	V-P	V-O	V-N	V-M	V-L	V-K	V-J	V-I	V-H	V-G	V-F	V-E	V-D	V-C	V-B	V-A	V-Z	V-Y	V-X</

ACKNOWLEDGMENTS

The HIV Sequence Database and Analysis Project is funded by the Vaccine and Prevention Research Program of the AIDS Division of the National Institute of Allergy and Infectious Diseases (Dr. James Bradac, Project Officer) through an interagency agreement with the U.S. Department of Energy.

We thank our editors, the many researchers who have made their sequences available prior to publication, and authors who help by contributing to our review section.

The Cover



A schematic representation of the activation mechanism of latent proviruses by NF- κ B and Tat during T-cell activation. From: Karn J, Tat, a novel regulator of HIV transcription and latency, Page 2 of this Compendium.

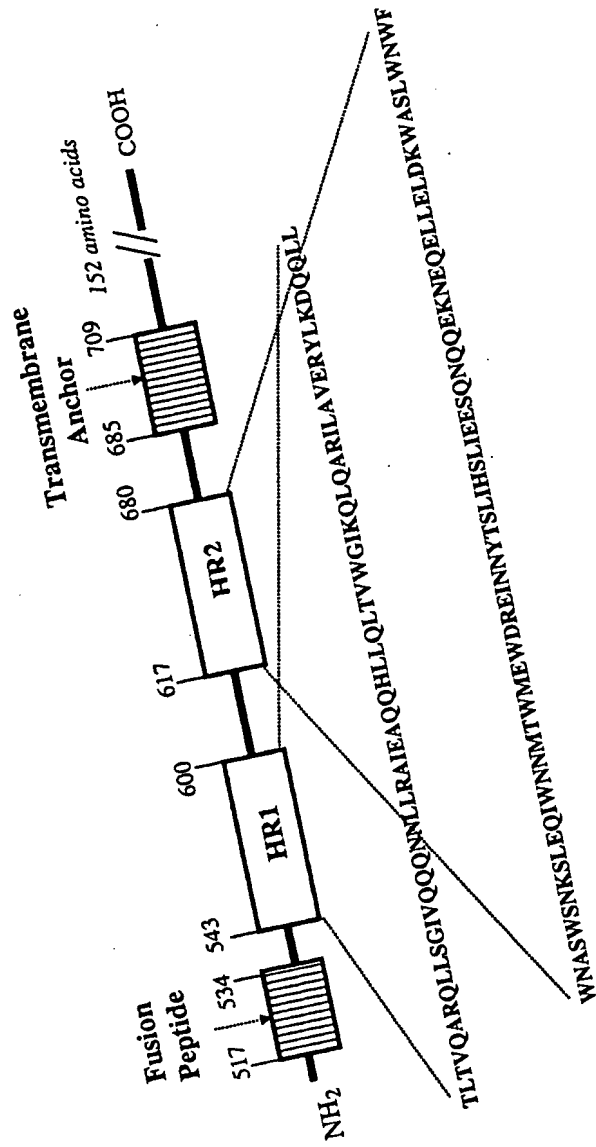
Citing this publication

We have simplified the name of this, our annual publication. Formerly known as "Human Retroviruses and AIDS" it should now be cited simply as *HIV Sequence Compendium 2000*, Kuiken C, Foley B, Hahn B, Marx P, McCutchan F, Mellors J, Mullins J, Wolinsky S, and Korber B, editors. Published by Theoretical Biology and Biophysics Group, Los Alamos National Laboratory.

assemble in solution into trimers. For example, SEQ ID NO:23 comprises the amino acid sequence of a native sequence when compared to SEQ ID NO:32 which comprises the amino acid sequence of a synthetic peptide of the present invention.

The term "reactive functionality", when used herein for purposes of the specification and claims, means a chemical group or chemical moiety that is capable of forming a covalent bond and/or is protective (e.g., protects peptide derivatives from reacting with themselves). With respect to chemical groups, a reactive functionality is known to those skilled in the art to comprise a group that includes, but is not limited to, maleimide, thiol, carboxy, phosphoryl, acyl, hydroxyl, acetyl, hydrophobic, amido, dansyl, fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), sulfo, a succinimide, a thiol-reactive, an amino-reactive, a carboxyl-reactive, and the like. A chemical moiety may comprise a linker. Linkers are known to refer to a compound or moiety that acts as a molecular bridge to operably link two different molecules (e.g., a wherein one portion of the linker binds to a peptide according to the present invention, and wherein another portion of the linker binds to a macromolecular carrier or another antiviral peptide known to inhibit HIV transmission to a target cell). The two different molecules may be linked to the linker in a step-wise manner. There is no particular size or content limitations for the linker so long as it can fulfill its purpose as a molecular bridge. Linkers are known to those skilled in the art to include, but are not limited to, chemical chains, chemical compounds (e.g., reagents), and the like. The linkers may include, but are not limited to, homobifunctional linkers and heterobifunctional linkers. Heterobifunctional linkers, well known to those skilled in the art, contain one end having a first reactive functionality to specifically link a first molecule, and an opposite end having a second reactive functionality to specifically link to a second molecule. It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, Ill.), may be employed as a linker with respect to the present invention. Depending on such factors as the molecules to be linked, and the conditions in which the linking is performed, the linker may vary in length and composition for optimizing such properties as preservation of biological function stability, resistance to certain chemical and/or temperature parameters, and of sufficient stereo-selectivity or size. For example, the linker should not significantly interfere with the ability of the synthetic peptide according to the present invention (to which it is linked) to function as an inhibitor of either or both of HIV fusion and HIV transmission to a target cell. A preferred reactive functionality

FIG. 1



HIV-DERIVED HR1 PEPTIDES MODIFIED TO FORM STABLE TRIMERS, AND THEIR USE IN THERAPY TO INHIBIT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS

This application claims the benefit of the U.S. Provisional Application 60/414,514 filed on 27 September 2002.

FIELD OF THE INVENTION

The present invention relates to synthetic peptides derived from the HR1 region of gp41, trimers formed therefrom, and their uses in anti-HIV therapy as antiviral agents to inhibit transmission of HIV (Human Immunodeficiency Virus) to target cells. More particularly, the present invention comprises a family of synthetic peptides which contain one or more site-specific amino acid substitutions (as compared to the native sequence) which uniquely result in a change in the oligomerization state in solution to self-association into predominately a trimeric form in forming a coiled coil, and may further stabilize such trimers formed.

BACKGROUND OF THE INVENTION

It is now well known that cells can be infected by HIV through a process by which fusion occurs between the cellular membrane and the viral membrane. The generally accepted model of this process is that the viral envelope glycoprotein complex (gp120/gp41) interacts with cell surface receptors on the membranes of the target cells. Following binding of gp120 to cellular receptors (e.g., CD4 in combination with a chemokine co-receptor such as CCR-5 or CXCR-4), induced is a conformational change in the gp120/gp41 complex that allows gp41 to insert into the membrane of the target cell and mediate membrane fusion.

The amino acid sequence of gp41, and its variation among different strains of HIV, is well known. FIG.1 is a schematic representation of the generally accepted functional domains of gp41 (note the amino acid sequence numbers may vary slightly depending on the HIV-1 strain). The fusion peptide (fusogenic domain) is believed to be involved in insertion into and disruption of the target cell membrane. The transmembrane domain, containing the transmembrane anchor sequence, is located at the C-terminal end of the protein. Between the fusion peptide and transmembrane anchor are two distinct regions, known as heptad repeat (HR) regions, each region having a plurality of heptads. The HR1 region, nearer to the N-terminal end of the protein than the HR2 region as depicted in FIG.1, has been generally described as comprising an amino acid

sequence having the sequence of SEQ ID NO:1. However, due to naturally occurring polymorphisms, the amino acid sequence of the HR1 region of HIV-1 gp41 may vary slightly, depending on the viral strain from which the amino acid sequence was deduced. The amino acid sequence comprising the HR1 region is one of the most highly conserved regions in the HIV-1 envelope protein (Shu et al., 1999, *Biochemistry*, 38:5378-5385). The other region, HR2, is also depicted in FIG.1 wherein the amino acid numbering corresponds to the amino acid sequence of gp160 in strain III B. The HR regions are known to have a plurality of 7 amino acid residue stretches or "heptads" (the 7 amino acids in each heptad designated "a" through "g"), wherein the amino acids in the "a" position and "d" position are generally hydrophobic. Also present in each HR region is one or more leucine zipper-like motifs (also referred to as "leucine zipper-like repeats"), each comprising an 8 amino acid sequence initiating with, and ending with an isoleucine or leucine. Most frequently, the HR2 region has just one leucine zipper like-motif, whereas the HR1 region has five leucine zipper-like motifs. Heptad repeats and leucine zipper-like motifs are amino acid sequences that contribute to formation of a coiled coil structure of gp41, and of a coiled coil structure of peptides derived from the HR regions. Generally, coiled coils are known to be comprised of two or more helices that wrap around each other in forming oligomers, with the hallmark of coiled coils being a heptad repeat of amino acids with a predominance of hydrophobic residues at the first ("a") and fourth ("d") positions, charged residues frequently at the fifth ("e") and seventh ("g") positions, and with the amino acids in the "a" position and "d" position being primary determinants that influence the oligomeric state and strand orientation (see, e.g., Akey et al., 2001, *Biochemistry*, 40:6352-60).

It was discovered that peptides derived from either the HR1 region ("HR1 peptides") or HR2 region ("HR2 peptides") of HIV-1 gp41 inhibit transmission of HIV to host cells both in *in vitro* assays and in *in vivo* clinical studies (see, e.g., Wild et al., 1994, *Proc. Natl. Acad. Sci. USA*, 91:9770-9774; U.S. Patent Nos. 5,464,933 and 5,656,480 licensed to the present assignee; and Kilby et al., 1998, *Nature Med.* 4:1302-1306. See also, e.g., U.S. Patent Nos. 6,258,782 and 6,348,568 assigned to the present assignee. The disclosures of these patents are herein incorporated by reference). More particularly, HR1 peptides exemplified by DP107 (also known as T-21, a synthetic peptide having the amino acid sequence of SEQ ID NO:2) blocked infection of T cells with 50% effective concentration values (EC50) of 1 µg/ml (see, e.g., Lawless et al., 1996, *Biochemistry*, 35:13697-13708). Sedimentation equilibrium experiments indicated

that, in solution, T-21 peptide exists in a monomer/ dimer/tetramer equilibrium (e.g., at concentrations of 5 μ M or less, with predominately tetramers at high concentrations of peptide (e.g., 10 μ M or more). A structural interaction occurring between a HR2 peptide and HR1 peptide has been observed when HR1 peptide is tetrameric (Lawless et al., *supra*). However, the generally accepted model of gp41 suggests that the gp41 core exists as a six helix bundle comprised of three N-terminal (HR1) regions forming a parallel trimeric coiled coil, where three C-terminal (HR2) regions pack in an antiparallel orientation into the hydrophobic grooves on the surface of the trimeric coiled coil (see, e.g., Shu et al., 1999, *Biochemistry* 38:5378-5385; Root et al., 2001, *Science* 291:884-888, and U.S. Patent No. 6,150,088). Accordingly, as compared to monomeric or tetrameric structures, trimers formed from self-assembly of synthetic peptide may provide a structure that acts more like the trimeric HR1 region in the *in vivo* binding interactions between the trimeric HR1 region and trimeric HR2 region of HIV gp41.

Thus, there is a need for additional compounds (particularly synthetic peptides self-assembled into trimeric form) which can interfere with the interaction of the various domains of gp41 involved in oligomerization and with the changes that gp41 undergoes which are necessary to effect fusion, thereby inhibiting the fusion of HIV gp41 to a target cell membrane.

SUMMARY OF THE INVENTION

The present invention relates to synthetic peptides derived from the HR1 region of HIV-1 gp41 wherein the synthetic peptides contain one or more site-specific amino acid substitutions (as compared to the native sequence of that HR1 region of HIV-1 gp41 or HR1 peptide derived therefrom), in one or more of the plurality of heptads of the peptide, which unexpectedly result in a change in the oligomerization state in solution to self-association into predominately a trimeric form ("self-associates" or "self-assembles" "into trimers"). Also provided are trimers formed from synthetic peptide.

In another object of the invention, provided are synthetic peptides derived from the HR1 region of HIV-1 gp41 which, in addition to containing one or more site-specific amino acid substitutions in one or more of the plurality of heptads which result in self-assembly into a trimeric form, also contains a plurality of amino acid substitutions which unexpectedly stabilize such trimers formed. Also provided are trimers formed from synthetic peptide.

In another object of the present invention, provided are synthetic peptides

	10	20	30	40
T-21	--NNLLRAIEAQQHLLQLTVWGIKQLQARILAVEERYLKDQ			
Gp41bru.pro	QQ			Q
Gp41hxb2.PRO	QQ			Q
PNL4-3 gp41.PRO	QQ			Q
Ug273-A.pro	QQS	K	L	R.Q
Us2-B.pro	QQ		V	Q
Ug268-C.pro	QQ	M	T.V.I	Q.Q
Se365-D.pro	QQ			R.Q
CM240-E.pro	QQS		V	K
Bz126-F.pro	QQ		V	Q.Q
HH8793-G.pro	QQS		V.L	R.Q
ENV_HV1BN	QQ	M	M.E	V.Q
ENV_HV1C4	QQ	K		Q
ENV_HV1KB	QQ	D	V	Q
_VCLJH00	QQ	K		Q
ENV_HV1B8	QQ	G		Q
ENV_HV1Z8	QQ	M	V	S.Q
1	QQT	M.K	V	Q
2	QQTS		V	R.Q
3	QQ	D.M	V.L.G	Q.Q
4	QQ	M.M	V	R.Q
5	QQS	M.L.MV	V	Q
6	QQS	M.M	V	Q
7	QQX	M	V.L	R.Q
8	QQ	D.G.D.P	W.V	RG.Q
9	QQ	S.Q	RM.V	Q
10	QQ	D	R.V.L	R.Q
11	QQT	M	S.V	Q
12	QRS	K	QMWR.F	L.Q
13	QQ	M	R.V	I.Q
14	QQS		PG	Q
15	QQ		V.K	R.Q
16	ER	K.R.M	V	S.Q
17	HQS		V	R.Q
18	QQ	D.G.D.P	V.V	RG.Q

FIG. 2

	abcd	f	g	abcde	def	g		
QARQLLSGI	VQQQNNLL	RAI	EAQQHLLQLTVWGI	KQLQARI	LAVERYLK		SEQ ID NO:23	
QARQLLSGI	VQQQNNLL	RAI	EAQQHALQATVWGI	KQLQARI	LAVERYLK		SEQ ID NO:32	
QARQLVSGI	VQQQNNI	LRALEATQHAYQALVWGV	KQLQARVLA	LEERYIK			SEQ ID NO:35	
QI	RQLLSGI	VQQQNNLL	RAI	EAQHALQAI	VWGI	KQLQARI	LAVERYLK	SEQ ID NO:36
QQQNNLL	RAI	EAQQHLLQLTVWGI	KQLQARI	LAVERYLK	DDQ	SEQ ID NO:27		
QQQNNLL	RAI	EAQQHLLQLTAWGI	KQLQARI	LAVERYLK	DDQ	SEQ ID NO:29		
QQQNNLL	RAI	EAQQHLLQLTVAGI	KQLQARI	LAVERYLK	DDQ	SEQ ID NO:30		

FIG. 3

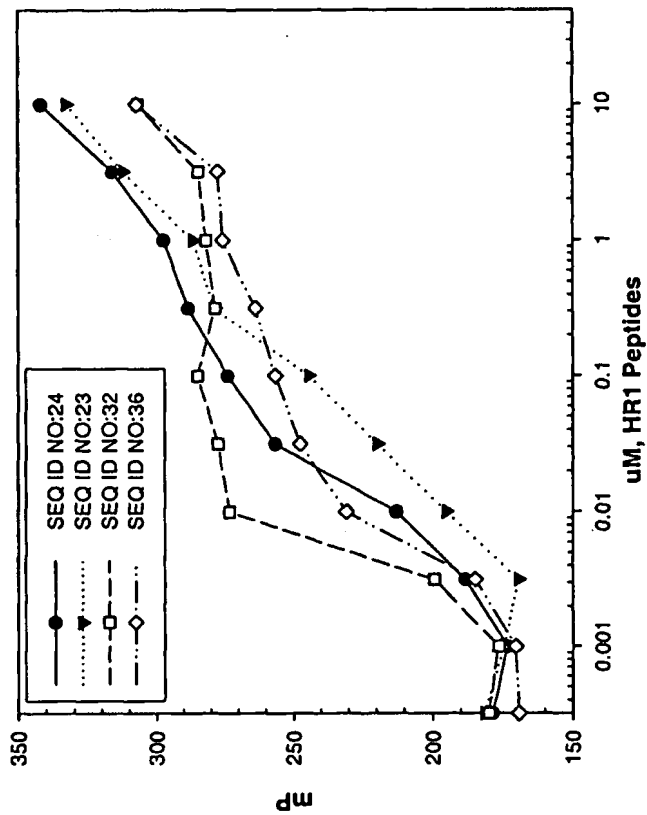


FIG. 4

HIV-1/SIVcpz proteins

HIV-1/SIVcpz
proteins[illegible]

<!--StartFragment-->RESULT 6

AA89779

ID AAY89779 standard; peptide; 41 AA.

XX

AC AAY89779;

XX

DT 23-MAY-2000 (first entry)

XX

DE Core polypeptide fragment T No. 1345.

XX

KW Retrovirus; hybrid polypeptide; enhancer; gp41; envelope protein; HIV-1;

KW HIV-2; SIV; pharmacokinetic; half-life; growth factor; cytokine; viral;

KW anti-fusogenic; differentiation factor; interleukin; interferon;

KW colony stimulating factor; hormone; angiogenic factor.

XX

OS Unidentified.

XX

PN WO9959615-A1.

XX

PD 25-NOV-1999.

XX

PF 20-MAY-1999; 99WO-US011219.

XX

PR 20-MAY-1998; 98US-00082279.

XX

PA (TRIM-) TRIMERIS INC.

XX

PI Barney S, Guthrie KI, Merutka G, Anwer MK, Lambert DM;

XX

DR WPI; 2000-136792/12.

XX

PT A new hybrid polypeptide with enhanced pharmacokinetic properties

PT comprises enhancer sequence.

XX

PS Disclosure; Page 44; 124pp; English.

XX

CC The invention relates to hybrid polypeptides comprising enhancer peptide
CC sequence linked to core polypeptides. The enhancer polypeptides are
CC derived from various retroviral envelope (gp41) protein sequences,
CC especially from HIV-1, HIV-2 and SIV. The enhancer peptides enhance the
CC pharmacokinetic properties such as increasing the half-life of any core
CC polypeptide that they are linked to. The core polypeptides are any
CC polypeptide that may be introduced into a living system and that can
CC function as a pharmacologically useful peptide for the treatment or
CC prevention of a disease. The core polypeptides are bioactive peptides
CC selected from a growth factor, cytokine, differentiation factor,
CC interleukin, interferon, colony stimulating factor, hormone or angiogenic
CC factor. The peptides of the invention can be used for inhibiting viral
CC infection and can be used in anti-viral and anti-fusogenic treatments.
CC Sequences AAY88651-Y90055 represent core polypeptide fragments that can
CC be used in the invention. Some sequences among those indicated also
CC comprise enhancer fragments at terminal ends and form hybrid polypeptides

XX

SQ Sequence 41 AA;

Query Match 98.0%; Score 199; DB 3; Length 41;

Best Local Similarity 97.6%; Pred. No. 4.6e-18;

Matches 40; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

efgabcdeF

QY 1 QQQNLLRAIEAQHLLQLTAWGIKQLQARILAVERYLKDQ 41 (seq 29)

|||||

Db 1 QQQNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ 41

PA/WT

<!--EndFragment-->

<210> SEQ ID NO 29

<211> LENGTH: 41

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 29

Gln Gln Gln Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu
1L Q L T 5 A W 10 15
Leu Gln Leu Thr Ala Trp Gly Ile Lys Gln Leu Gln Ala Arg Ile Leu
20 25 30
Ala Val Glu Arg Tyr Leu Lys Asp Gln
35 40

e f g
Q Q H L

<!--StartFragment-->RESULT 8

ABB01187

ID ABB01187 standard; peptide; 41 AA.

XX

AC ABB01187;

XX

DT 11-SEP-2003 (revised)

DT 06-AUG-2003 (revised)

DT 03-JAN-2002 (first entry)

XX

DE Viral DP178/107-like region peptide T1345.

XX

KW Human immunodeficiency virus; HIV; respiratory syncytial virus; RSV;
KW virucide; heptad repeat region; transmembrane protein; gp41; HR1; HR2;
KW infection.

XX

OS Viruses.

XX

FH Key Location/Qualifiers

FT Modified-site 1

FT /note= "N-terminal is substituted by Ac"

FT Modified-site 41

FT /note= "C-terminal amide"

XX

PN WO200164013-A2.

XX

PD 07-SEP-2001.

XX

PF 07-FEB-2001; 2001WO-US003988.

XX

PR 29-FEB-2000; 2000US-00515965.

XX

PA (TRIM-) TRIMERIS INC.

XX

PI Antczak JB, Delmedico MK, Erickson JB, Lambert DM, Sista P;

XX

DR WPI; 2001-514829/56.

XX

PT Heptad repeat region peptide analogs useful for inhibiting virus/cells
PT fusion, useful for treating HIV and Respiratory Syncytial Virus
PT infection.

XX

PS Disclosure; Page 57; 587pp; English.

XX

CC The invention relates to isolated analogues of the heptad repeat region
CC peptides DP178 and DP107. DP178 and DP107 correspond to amino acids 638-
CC 673 (heptad repeat region HR2) and 558-595 (heptad repeat region HR1)
CC respectively, of HIV-1LAI transmembrane protein gp41. The HR1 and HR2
CC regions of proteins interact non-covalently with each other and/or with
CC peptides derived from them. This interaction is required for normal
CC infectivity of viruses such as RSV and HIV. The heptad repeat region
CC peptide analogues may be used to inhibit respiratory syncytial virus
CC (RSV) infection in a cell. They may also be used to inhibit HIV
CC infection. The present sequence is a peptide provided in the
CC specification. (Updated on 06-AUG-2003 to correct OS field.) (Updated on
CC 11-SEP-2003 to standardise OS field)

XX

SQ Sequence 41 AA;

Query Match 98.0%; Score 199; DB 4; Length 41;

Best Local Similarity 97.6%; Pred. No. 4.6e-18;

Matches 40; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

Qy 1 QQQNNLLRAIEAQQHLLQLTAWGIKQLQARILAVERYLKDQ 41

|||||

Db 1 QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ 41

<!--EndFragment-->

<!--StartFragment-->RESULT 10

AAU13733

ID AAU13733 standard; peptide; 41 AA.

XX

AC AAU13733;

XX

DT 21-NOV-2001 (first entry)

XX

DE DP178-like/DP107-like peptide T-1345.

XX

KW Anti-retroviral; DP178-like; DP107-like; transmembrane protein gp41;

KW antifusogenic; antiviral; HIV transmission; mutant; mutein.

XX

OS Human immunodeficiency virus 1; isolate LAI.

OS Synthetic.

XX

FH Key Location/Qualifiers

FT Modified-site 1

FT /note= "N-terminal is substituted by Ac"

FT Modified-site 41

FT /note= "C-terminal amide"

XX

PN WO200151673-A2.

XX

PD 19-JUL-2001.

XX

PF 05-JUL-2000; 2000WO-US035727.

XX

PR 09-JUL-1999; 99US-00350841.

XX

PA (TRIM-) TRIMERIS INC.

XX

PI Jeffs P, Lackey JW, Erickson JB, Lawless MK, Merutka G;

XX

DR WPI; 2001-442157/47.

XX

PT Identifying a compound that inhibits the formation of or disrupts a
PT DP107/DP178 complex, especially compounds with antifusogenic, antiviral
PT or intracellular modulatory activity, by detecting the formation of a
PT DP107/DP178 complex.

XX

PS Disclosure; Page 76; 259pp; English.

XX

CC The present invention relates to peptides which exhibit anti-retroviral
CC activity. The peptides of the invention (AAU12559-AAU14009) comprise
CC DP178-like and DP107-like peptides. The DP178 peptide corresponds to
CC amino acids 639-673 of the transmembrane protein gp41 from human
CC immunodeficiency virus 1 (HIV-1) isolate LAI. The DP107 peptide
CC corresponds to amino acids 558-595 of gp41 from HIV-1LAI. The invention
CC also relates to a method of identifying compounds that inhibit the
CC formation of or disrupts a DP107/DP178 complex. The method comprises
CC detecting the formation of a DP107/DP178 complex, both in the presence or
CC absence of a test compound, in a reaction mixture containing DP107 and
CC DP178 peptides. The method is useful for identifying compounds, including
CC small molecule compounds, which may themselves exhibit antifusogenic,
CC antiviral or intracellular modulatory activity. The DP178-like/DP107-like
CC peptides are useful to inhibit human and non-human retroviral,
CC particularly HIV, transmission to uninfected cells. The present sequence
CC represents one of the DP178-like/DP107-like peptides of the invention

XX

SQ Sequence 41 AA;

Query Match 98.0%; Score 199; DB 4; Length 41;

Best Local Similarity 97.6%; Pred. No. 4.6e-18;

Matches 40; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

Qy 1 QQQNLLRAIEAQHLLQLTAWGIKQLQARILAVERYLKDQ 41

Db 1 QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVEERYLKDQ 41

<!--EndFragment-->

<!--StartFragment-->RESULT 11

ADE02656

ID ADE02656 standard; peptide; 41 AA.

XX

AC ADE02656;

XX

DT 29-JAN-2004 (first entry)

XX

DE Hybrid polypeptide pharmacokinetic enhancer peptide, SEQ ID No 1163.

XX

KW hybrid; enhancer; anti-fusogenic; antiviral; virucide; antidiabetic;

KW pharmacokinetic; fusogenic; insulin; diabetes.

XX

OS Unidentified.

XX

FH Key Location/Qualifiers

FT Modified-site 1

FT /note= "Residue is modified by acetyl group"

FT Modified-site 41

FT /note= "C-terminal amide"

XX

PN US6348568-B1.

XX

PD 19-FEB-2002.

XX

PF 20-MAY-1999; 99US-00315304.

XX

PR 20-MAY-1998; 98US-00082279.

XX

PA (TRIM-) TRIMERIS INC.

XX

PI Barney S, Guthrie KI, Merutka G, Anwer MK, Lambert DM;

XX

DR WPI; 2002-424396/45.

XX

PT New hybrid polypeptide for modulating fusogenic events for e.g. antiviral

PT activity, has enhancer peptide sequence derived from retroviral envelope

PT protein sequences linked to core polypeptide e.g. therapeutic protein.

XX

PS Disclosure; SEQ ID NO 1163; 70pp; English.

XX

CC The invention relates to a novel hybrid polypeptide comprising an
CC enhancer peptide sequence linked to a core polypeptide. The enhancer
CC peptide sequence comprises WQEWQKI or WASLWEWF. The invention also
CC includes novel peptides that exhibit anti-fusogenic activity, antiviral
CC activity and/or ability to modulate intracellular processes. The novel
CC hybrid polypeptide has virucide and antidiabetic activity. The enhancer
CC peptide sequence enhances pharmacokinetic properties of any core
CC polypeptide, for example, a polypeptide useful for the treatment or
CC prevention of a disease, or an imaging agent useful for imaging
CC structures in vivo. The core polypeptides and hybrid polypeptides are
CC useful for modulating fusogenic events and exhibit antifusogenic or
CC antiviral activity. The novel hybrid polypeptide is useful for decreasing
CC viral infection and modulating intracellular processes involving coiled-
CC coil peptide interactions. The novel hybrid polypeptide comprises insulin
CC or its fragment, so the core polypeptide is useful for ameliorating the
CC symptoms of forms of diabetes. The novel hybrid polypeptide is also
CC useful as a part of prognosis for preventing disorders including fusion
CC events and viral infection that involves cell-cell and/or virus-cell
CC fusion, and for diagnosis and in vivo imaging methods. This sequence
CC represents an enhancer peptide of the invention.

XX

SQ Sequence 41 AA;

Query Match 98.0%; Score 199; DB 5; Length 41;

Best Local Similarity 97.6%; Pred. No. 4.6e-18;

Matches 40; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

Qy 1 QQQNLLRAIEAQHLLQLTAWGIKQLQARILAVEYLKDQ 41

|||||

Db 1 QQQNLLRAIEAQHLLQLTVWGIKQLQARILAVEYLKDQ 41

<!--EndFragment-->

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<!--StartFragment-->RESULT 1
US-09-082-279B-1163
; Sequence 1163, Application US/09082279B
; Patent No. 6258782
; GENERAL INFORMATION:
; APPLICANT: Barney, Shawn
; APPLICANT: Guthrie, Kelly
; APPLICANT: Merutka, Gene
; APPLICANT: Anwer, Mohmed
; APPLICANT: Lambert, Dennis
; TITLE OF INVENTION: HYBRID POLYPEPTIDES WITH ENHANCED
; TITLE OF INVENTION: PHARMACOKINETIC PROPERTIES
; FILE REFERENCE: 7872-043
; CURRENT APPLICATION NUMBER: US/09/082,279B
; CURRENT FILING DATE: 1998-05-20
; NUMBER OF SEQ ID NOS: 1515
; SOFTWARE: FastSEQ for Windows Version 3.0
; SEQ ID NO 1163
; LENGTH: 41
; TYPE: PRT
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Core polypeptide
US-09-082-279B-1163
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Query Match          98.0%; Score 199; DB 2; Length 41;
Best Local Similarity 97.6%; Pred. No. 4.1e-20;
Matches 40; Conservative 0; Mismatches 1; Indels 0; Gaps 0;
```

```
Qy      1 QQQNLLRAIEAQQHLLQLTAWGIKQLQARILAVERYLKDQ 41
          ||||||||||||||||||| |||||||||||||||||||
Db      1 QQQNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ 41
```

```
<!--EndFragment-->
```

<!--StartFragment-->RESULT 11

AAB24105

ID AAB24105 standard; protein; 50 AA.

XX

AC AAB24105;

XX

DT 12-SEP-2003 (revised)

DT 29-JAN-2001 (first entry)

XX

DE HIV-1 gp41 NHR region amino acid sequence SEQ ID NO:2.

XX

KW HIV-1; human immunodeficiency virus; human; epitope; gp41; MAb;

KW monoclonal antibody; antiviral; antiHIV; infection; inhibition;

KW replication.

XX

OS Human immunodeficiency virus 1.

XX

PN WO200055377-A1.

XX

PD 21-SEP-2000.

XX

PF 15-MAR-2000; 2000WO-US006771.

XX

PR 17-MAR-1999; 99US-0124907P.

PR 14-MAR-2000; 2000US-00525874.

XX

PA (NYBL-) NEW YORK BLOOD CENT INC.

PA (JIAN/) JIANG S.

PA (DEBN/) DEBNATH A K.

XX

PI Jiang S, Debnath AK;

XX

DR WPI; 2000-656011/63.

XX

PT Screening assay for antiviral compounds targeted to HIV-1 gp41 core
PT structure involves utilizing conformation-specific monoclonal antibody,
PT which is reactive with fusion active gp41 of the virus.

XX

PS Disclosure; Fig 2; 79pp; English.

XX

CC The present invention describes a method for screening (M1) an antiviral
CC compound (AC) targeted to the HIV-1 gp41 core structure. The method
CC involves capturing polyclonal antibodies (PAB) directed against trimer of
CC heterodimer (A) which contains N- and C-peptide (NP,CP) onto a solid-
CC phase, to form a PAB-coated solid-phase that is added with mixture of NP,
CC CP, and AC, adding monoclonal antibody (MAb) directed against (A) and
CC measuring the binding of MAb. The antivirals identified by the method are
CC useful for inhibiting HIV-1 replication or infectivity in cells, in
CC patients and for treating the patients infected with HIV-1. The method
CC distinguishes the anti-HIV-1 agents targeting the gp41 core domain from
CC those having different targets. Since the residues located at the
CC interaction sites in both the N-terminal heptad repeat (NHR) and C-
CC terminal heptad repeat (CHR) regions of gp41 are highly conserved, the
CC antiviral agents targeted to the gp41 core are considered to have broader
CC specificity against infection by HIV strains than those targeted to
CC gp120. The present sequence represents the HIV-1 gp41 NHR region amino
CC acid sequence, which is used in the exemplification of the present
CC invention. (Updated on 12-SEP-2003 to standardise OS field)

XX

SQ Sequence 50 AA;

Query Match 96.6%; Score 224; DB 3; Length 50;

Best Local Similarity 95.9%; Pred. No. 3.9e-19;

Matches 47; Conservative 2; Mismatches 0; Indels 0; Gaps 0;

Qy 1 QARQLLSGIVQQQNLLRAIEAQQHLLQLTVFGIRQLQARILAVEERYLK 49

|||||:|:|||||

<!--EndFragment-->

<!--StartFragment-->

RESULT 11

AAB24105

ID AAB24105 standard; protein; 50 AA.

XX

AC AAB24105;

XX

DT 12-SEP-2003 (revised)

DT 29-JAN-2001 (first entry)

XX

DE HIV-1 gp41 NHR region amino acid sequence SEQ ID NO:2.

XX

KW HIV-1; human immunodeficiency virus; human; epitope; gp41; MAb;

KW monoclonal antibody; antiviral; antiHIV; infection; inhibition;

KW replication.

XX

OS Human immunodeficiency virus 1.

XX

PN WO200055377-A1.

XX

PD 21-SEP-2000.

XX

PF 15-MAR-2000; 2000WO-US006771.

XX

PR 17-MAR-1999; 99US-0124907P.

PR 14-MAR-2000; 2000US-00525874.

XX

PA (NYBL-) NEW YORK BLOOD CENT INC.

PA (JIAN/) JIANG S.

PA (DEBN/) DEBNATH A K.

XX

PI Jiang S, Debnath AK;

XX

DR WPI; 2000-656011/63.

XX

PT Screening assay for antiviral compounds targeted to HIV-1 gp41 core
PT structure involves utilizing conformation-specific monoclonal antibody,
PT which is reactive with fusion active gp41 of the virus.

XX

PS Disclosure; Fig 2; 79pp; English.

XX

CC The present invention describes a method for screening (M1) an antiviral
CC compound (AC) targeted to the HIV-1 gp41 core structure. The method
CC involves capturing polyclonal antibodies (PAB) directed against trimer of
CC heterodimer (A) which contains N- and C-peptide (NP,CP) onto a solid-
CC phase, to form a PAB-coated solid-phase that is added with mixture of NP,
CC CP, and AC, adding monoclonal antibody (MAb) directed against (A) and
CC measuring the binding of MAb. The antivirals identified by the method are
CC useful for inhibiting HIV-1 replication or infectivity in cells, in
CC patients and for treating the patients infected with HIV-1. The method
CC distinguishes the anti-HIV-1 agents targeting the gp41 core domain from
CC those having different targets. Since the residues located at the
CC interaction sites in both the N-terminal heptad repeat (NHR) and C-
CC terminal heptad repeat (CHR) regions of gp41 are highly conserved, the
CC antiviral agents targeted to the gp41 core are considered to have broader
CC specificity against infection by HIV strains than those targeted to
CC gp120. The present sequence represents the HIV-1 gp41 NHR region amino
CC acid sequence, which is used in the exemplification of the present
CC invention. (Updated on 12-SEP-2003 to standardise OS field)

XX

SQ Sequence 50 AA;

Query Match 96.6%; Score 224; DB 3; Length 50;

Best Local Similarity 95.9%; Pred. No. 3.9e-19;

Matches 47; Conservative 2; Mismatches 0; Indels 0; Gaps 0;

Db

|||||:|:|||||
1 QARQLSGIVQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLK 49

<!--EndFragment-->

<!--StartFragment-->

RESULT 12

AAV89334

ID AAV89334 standard; peptide; 51 AA.

XX

AC AAV89334;

XX

DT 23-MAY-2000 (first entry)

XX

DE Core polypeptide fragment T No. 865.

XX

KW Retrovirus; hybrid polypeptide; enhancer; gp41; envelope protein; HIV-1;

KW HIV-2; SIV; pharmacokinetic; half-life; growth factor; cytokine; viral;

KW anti-fusogenic; differentiation factor; interleukin; interferon;

KW colony stimulating factor; hormone; angiogenic factor.

XX

OS Unidentified.

XX

PN WO9959615-A1.

XX

PD 25-NOV-1999.

XX

PF 20-MAY-1999; 99WO-US011219.

XX

PR 20-MAY-1998; 98US-00082279.

XX

PA (TRIM-) TRIMERIS INC.

XX

PI Barney S, Guthrie KI, Merutka G, Anwer MK, Lambert DM;

XX

DR WPI; 2000-136792/12.

XX

PT A new hybrid polypeptide with enhanced pharmacokinetic properties

PT comprises enhancer sequence.

XX

PS Disclosure; Page 34; 124pp; English.

XX

CC The invention relates to hybrid polypeptides comprising enhancer peptide

CC sequence linked to core polypeptides. The enhancer polypeptides are

CC derived from various retroviral envelope (gp41) protein sequences,

CC especially from HIV-1, HIV-2 and SIV. The enhancer peptides enhance the

CC pharmacokinetic properties such as increasing the half-life of any core

CC polypeptide that they are linked to. The core polypeptides are any

CC polypeptide that may be introduced into a living system and that can

CC function as a pharmacologically useful peptide for the treatment or

CC prevention of a disease. The core polypeptides are bioactive peptides

CC selected from a growth factor, cytokine, differentiation factor,

CC interleukin, interferon, colony stimulating factor, hormone or angiogenic

CC factor. The peptides of the invention can be used for inhibiting viral

CC infection and can be used in anti-viral and anti-fusogenic treatments.

CC Sequences AAV88651-Y90055 represent core polypeptide fragments that can

CC be used in the invention. Some sequences among those indicated also

CC comprise enhancer fragments at terminal ends and form hybrid polypeptides

XX

SQ Sequence 51 AA;

Query Match 96.6%; Score 224; DB 3; Length 51;

Best Local Similarity 95.9%; Pred. No. 4e-19;

Matches 47; Conservative 2; Mismatches 0; Indels 0; Gaps 0;

Qy 1 QARQLLSGIVQQQNNLLRAIEAQHLLQLTVFGIRQLQARILAVERYLK 49

|||||:|:|||||

Db 1 QARQLLSGIVQQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLK 49

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<!--StartFragment-->RESULT 2
US-09-082-279B-745
; Sequence 745, Application US/09082279B
; Patent No. 6258782
; GENERAL INFORMATION:
; APPLICANT: Barney, Shawn
; APPLICANT: Guthrie, Kelly
; APPLICANT: Merutka, Gene
; APPLICANT: Anwer, Mohmed
; APPLICANT: Lambert, Dennis
; TITLE OF INVENTION: HYBRID POLYPEPTIDES WITH ENHANCED
; TITLE OF INVENTION: PHARMACOKINETIC PROPERTIES
; FILE REFERENCE: 7872-043
; CURRENT APPLICATION NUMBER: US/09/082,279B
; CURRENT FILING DATE: 1998-05-20
; NUMBER OF SEQ ID NOS: 1515
; SOFTWARE: FastSEQ for Windows Version 3.0
; SEQ ID NO 745
; LENGTH: 51
; TYPE: PRT
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Core polypeptide
US-09-082-279B-745

```

```

Query Match          96.6%; Score 224; DB 2; Length 51;
Best Local Similarity 95.9%; Pred. No. 3.3e-23;
Matches 47; Conservative 2; Mismatches 0; Indels 0; Gaps 0;

```

```

Qy      1 QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVFGIRQLQARILAVERYLK 49
        |||||||||||||||||||||||||||||||||||:|:|||||||||
Db      1 QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLK 49

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